REMARKS

Claims 1-35, 51 and 57 have been cancelled.

Claims 36, 38 and 39 are amended.

Claims 60-73 are withdrawn from consideration by the examiner. Thus, claims 36-50 and 52-56, 58 and 59 remain active and under consideration.

Applicants wish to thank Examiner Li for the recent helpful and courteous discussion with their U.S. representative, Mr. William Beaumont. Consistent with the remarks made during the discussion, Applicants have amended the claims and offer the additional remarks below.

For the examiner's convenience, it is emphacized that claim 36 now recites that the transgenic mouse produces no immunoglobulins M. Support for amended claim 36 in may be found in the overall specification and drawings, and, in particular, on figures 1 and 9, and page 7, lines 11-15 and 19-23, and the examples. See page 27, lines 12-23 and page 37, lines 10-33. No new matter has been added.

Additionally, at the outset, it is noted that arguments/rationale for the patentability of the targeting vector of claims 53-56 and 58 are set forth at page 7, paragraphs 2 and 3; and page 13, paragraphs 4 and 6 of this response, i.e., in the "REMARKS" section continuing hereinbelow.

Claims 53-56, 58 and 59 stand rejected under 35 USC 103 (a) as being unpatentable over Green *et al* (USP 7,547,817) in view of Luby *et al* (J. Exp. Med. 2001; 193: 159-168).

However, the rejection of claims 53-56, 58 and 59 under 35 USC 103(a) over Green *et al.* (US 7,547,817) in view of Luby *et al.* (J. Exp. Med., 2001, 193, 159-68) is respectfully traversed as the cited references fail to disclose or suggest all the elements of the claimed invention, or even provide a reasonable expectation of success for the claimed invention. Also, the prior art teaches away from the claimed invention and, moreover, the claimed invention affords unexpected results. This is also true for all of claims 36-50, 52-56, 58 and 59.

Applicants note that Green is considered by the Examiner as differing from the present claims in that "*the inserted CH gene operably linked to a non-cognate switch sequence whereas a preferred embodiment of instantly claimed transgenic animal does not contain a switch sequence. However, it is noted instant claims embrace a transgene comprising a non-cognate switch sequence*" (page 4 of the previous Office Action).

However this is not true.

It is well-established that a reference must be assessed on the basis of its content as a whole. Furthermore, a reference should always be considered for everything it would have fairly

taught a person having ordinary skill in the art, i.e., even if the reference supports the patentability of a claimed invention.

In addition, prior art documents and the application do need to disclose what is already known in the art and should be read giving the words the meaning and scope which they normally have in the relevant art. It is well-established that a patent specification need not be a "production specification".

Having noted the above prerequisite remarks, Applicants now turn to an elucidation of the differences between the claimed invention and the cited references. These remarks will clearly explain how and why the claimed transgenic mouse is patentably distinct from the what is disclosed in the cited references. Of course, the term "transgenic" indicates that a donor gene has been spliced into a host strand of DNA, the donor gene and host DNA arising from different organisms. See Medical Dictionary, page excerpt attached to this response.

- *Green et al.*

Green discloses a transgenic mouse containing an unrearranged human immunoglobulin heavy chain (IgH) transgene comprising human VH genes, all the human D elements, all human J elements, **human Sμ, human Cμ** and human Cδ from human chromosome 14, and an additional human constant region gene encoding the desired IgH isotype, operably linked to an heterologous or non-cognate switch region (column 5, line 65 to column 6, line 3; column 6, lines 21 to 36).

In a specific embodiment, the heterologous switch region is a mouse switch region, operably linked to a human Cα gene (column 6, lines 40-43).

The exemplified transgenic mouse strains (column 12, line 36 to column 13 line 14; examples 1 to 33) which are cited by the Examiner (page 3 of the Office Action) comprise an unrearranged human IgH transgene derived from the human IgH Yeast Artificial Chromosome (YAC), yH1C (column 12, lines 49 and 51, column 13, lines 7-9). yH1C comprises 66 human VH, all the human D elements, all human J elements, human Eμ, **human Sμ, human Cμ**, human Cδ, human Sγ2, human Cγ2, and a 4 kb fragment containing the mouse 3' enhancer element (column 10, lines 21-30).

Green et al discloses the targeted replacement on yH1C, in yeast (column 12, lines 48-55, column 13, lines 2 to 9; column 15, lines 13 to 44 and examples 1 to 5).
This targeted replacement consists of the following replacement on the YAC, yH1C:

(i) Replacement of the human Cγ2 on yH1C by another human CH gene (human Cγ1 or Cγ4; column 6, lines 55-62; column 12, line 56 to column 13, line 9; column 15, lines 13-44; examples 3, 4, 5 and 20 to 33 and figures 2 to 7) to obtain the recombinant YACs, yHG1, yHG4, yHG1/2 and yHG4/2, or

(ii) Replacement of the human Sγ2 and Cγ2 on yH1C with the murine Sγ1 and a human CH coding sequence (human Cγ1 or Cγ4; column 6, lines 43-50; column 12, lines 34 to 55; examples 1, 2, 5, 6 to 19; figures 1) to obtain the recombinant YACs yH2Bm and yH2Cm.

Therefore, Green et al disclose the replacement of human Cγ2 or human Sγ2 and Cγ2 by a human CH gene (Cγ1 or Cγ4).

In addition, the replacement disclosed by Green et al is in an unrearranged human IgH transgene.

Furthermore, the unrearranged human IgH transgene is introduced into the germline of the mouse (ES cells) using the IgH YACs mentioned above to produce a transgenic mouse having the transgene in its somatic and germ cells (column 2, lines 59-64; Column 5, Line 66 to Column 6, Line 3, Column 6, Lines 36-37; Column 7, lines 44-48; Column 9, Line 58 to Column 10, Line 42 and examples 6, 7, 13, 14, 20, 21, 27, 28).

The YACs are defined in column 9, lines 49-57, the exemplified YAC, yH1C, is disclosed in column 10, lines 21-42. As discussed already, yH1C contains a mega-sized unrearranged human IgH transgene and a 4 kb fragment containing the mouse 3' enhancer element, flanked by a left and a right arms carrying expression cassettes for yeast and mammalian selectable markers (column 10, lines 31-35), yeast elements, a bacterial origin of replication and selectable marker for replication and selection of the YAC vectors arms in bacteria (column 9, lines 49-55).

Therefore, the YAC which does not contain mouse 5' and 3' homology arm sequences flanking a targeted mouse locus is not a targeting vector.

For these reasons, the Green et al transgenic mouse contains a human IgH transgene which is not inserted at a targeted locus, *i.e.*, a human IgH transgene which is inserted at an unknown locus of the mouse genome (random insertion).

Green et al specify that to generate mice that produce human antibodies in the absence of endogenous antibodies (*i.e.* Xenomouse strains), the mice transgenic for the unrearranged human IgH transgene are bred onto a double-inactivated (DI) background, *i.e.*, with mice which are homozygous for gene-targeted inactivated mouse heavy and kappa light chain loci (column 6, lines 12-17; column 9, line 59 to column 10, line 20; column 16, line 58 to column 18, line 15 and examples 8, 22 and 29).

This means that the endogenous mouse IgH locus of the transgenic mouse is not modified and is functional (*i.e.*, the transgenic mouse produces mouse Ig heavy and light chains); it can be further inactivated by gene-targeted inactivation to generate Xenomouse strains that do not produce mouse antibodies.

Therefore, the human IgH transgene is at a locus of the transgenic mouse/Xenomouse

genome which is distinct from the endogenous mouse IgH locus.

The Xenomouse strains which have integrated said recombinant YACs in their somatic and germ cells comprise an unrearranged human IgH transgene comprising 66 human VH, all the human D elements, all human J elements, human Eμ, **human Sμ, human Cμ,** human Cδ and **a chimeric human CH gene in which class switch recombination between Sμ and the human Sγ2 or the mouse Sγ1 controls isotype-class switching from human IgM to the downstream human CH gene for the desired IgH isotype** (Cγ1 or Cγ4 in the exemplified transgenic mouse strains; column 6, lines 26-33; column 11, lines 55, 61; column 12, lines 53-55 and 59-60).

The human Sμ and Cμ which are upstream of the chimeric CH gene in the human IgH transgene are neither deleted and always functional in the Xenomouse. Therefore, the Xenomouse produces fully human IgM and undergo isotype class-switching from fully human IgM to fully human Ig of the desired isotype and the frequency of class switching increases during an immune response (column 5, lines 63-64; column 10, lines 16-20 and 61-62; column 22; lines 30-50; Examples 9, 16 (Tables 5 and 10 showing IgM+ B cells); Examples 10, 17 (Tables 6 and 11 showing human IgM and IgG antibodies production).

Therefore, Green et al disclose a **transgenic mouse (Xenomouse) which is totally different from the claimed transgenic mouse** in that:

(i) in the **Xenomouse**, **the human CH transgene** encoding the desired IgH isotype (Cγ, Cα) **is inserted in an unrearranged functional mega-sized human IgH transgene** which comprises 66 human VH, all the human D elements, all human J elements, human Eμ, **human Sμ, human Cμ**, human Cδ human Sγ2, human Cγ2, and a 4 kb fragment containing the mouse 3' enhancer element **and which is at a locus distinct from the endogenous mouse IgH locus**, **and the endogenous mouse IgH locus is inactivated**, whereas, in the **claimed transgenic mouse, the human CH transgene is inserted in the endogenous mouse IgH locus,**

(ii) in the **Xenomouse, the human CH transgene replaces the human Cγ2 or human Sγ2 and Cγ2 in the unrearranged human IgH transgene**, whereas in the **claimed transgenic mouse**, **the human CH transgene which replaces Sμ in the endogenous mouse IgH locus and is thus inserted between Eμ and Cμ abolishes the expression of Cμ and the production of IgM antibodies** (figure 1; page 7, lines 11-15 and page 27, lines 17-23 of the present application).

(iii)**the Xenomouse produces fully human IgM antibodies and fully human Ig antibodies of the desired isotype (IgG, IgA, IgE) upon isotype-class switching** whereas the **claimed transgenic mouse produces chimeric IgA antibodies whose heavy chains comprise a human constant region and a mouse variable region and no IgM** (figure 9; page 7, lines 11-15 and 19-23; page 27, lines 12-23; page 37, lines 10-33 of the present application).

In fact the only common feature between the Xenomouse and the claimed transgenic mouse

is the human CH transgene.

The Xenomouse does not have a human CH transgene inserted in the endogenous mouse IgH locus and does not have a human CH transgene that replaces the mouse Sμ in the endogenous mouse IgH locus.

The Xenomouse has an unrearranged mega-sized human IgH transgene and an endogenous mouse IgH locus which is inactivated. The Xenomouse has a human CH transgene that is inserted downstream of the human Sμ and human Cμ in the human IgH transgene, and that replaces the human Cγ2 or human Sγ2 and Cγ2 in the human IgH transgene.

As a consequence, the Xenomouse produces fully human IgM antibodies and IgG antibodies of the desired isotype but no mouse antibodies.

For producing Ig of the desired isotype (IgG, IgA, IgE), Green et al thus disclose a transgenic mouse which has a human IgH transgene and an inactivated endogenous mouse IgH locus.

Therefore, Green et al do not suggest a transgenic mouse, knock-in at the endogenous mouse IgH locus, which produces chimeric IgA, wherein the IgH chains have a human constant region and a mouse variable region

In accordance with a well established scientific principle in the art of immunology (See *Annex I,* previously presented with the response to the first Office Action), Green et al disclose that **B cell maturation, *in vivo*, requires the expression of membrane IgM on B cells surface and that the production of a selected antibody isotype, *in vivo*, requires the development of IgM producing B cells which subsequently undergo isotype class switching from IgM to the IgG or IgA, or IgE isoptypes** (see in particular the paragraphs entitled "*XenoMouse Development*", bridging columns 9 and 10; "*B cell Development*, column 10; "*Class Switching*", bridging columns 11 and 12).

For instance, Green et al describe that "*Successful B cell development in the bone marrow results in B cells expressing IgMκ or IgMλ on the cell surface. These IgM producing B cells form the primary immune repertoire and perform immune surveillance for recognition of foreign antigens. In the mouse or in humans, these IgM producing B cells can subsequently undergo isotype class switching from IgM to the IgG or IgA or IgE isotypes. The frequency of class switching increases during an immune response*" (column 10, lines 52-62).

As discussed already in the instant response and the previous response, the transgenic mice which are disclosed in Green et al have IgM producing B cells which subsequently undergo isotype class switching from IgM to IgG isoptype.

For instance, Green et al describe that: "*In addition, these mice produced fully human IgMκ and IgG2κ antibodies, and ultimately, hybridomas secreting antigen-specific high affinity fully human IgG2κ monoclonal antibodies with therapeutic potential were generated*" (column 10, lines 16-20).

Therefore, Green *et al* actually teach away from producing a transgenic mouse which produces no IgM.

- *Luby et al.*

Luby *et al* is cited as establishing at the time of present priority date, that it was well known in the art that μ switch tandem repeats (Sμ) is important but not required for antibody class switch (sentence bridging page 4 and page 5 of the instant Office Action).

Luby *et al* disclose only deleting Sμ in the endogenous mouse IgH locus to study the role of Sμ in antibody class switching (abstract and introduction).

The Sμ-deleted (ΔSμ) mouse was produced by standard gene targeting approaches (page 160, second paragraph and figure 1) as the claimed transgenic mouse. Therefore, the targeting construct comprises a selection marker gene flanked by two loxP sites (neo/loxP cassette), inserted between the two homology regions (see page 160, 1st column, lines 5-7 of second paragraph of Luby; figure 1 of the present application). Luby teaches that "*The chimeric transgenic mice that carried the targeted allele are mated to Cre recombinase transgenic mice in order to remove the neomycine cassette. This provided the ΔSμ allele that has one loxP site replacing Sμ*".

Luby *et al* disclose a standard gene-targeted deletion approach using a neo/loxP cassette which results in loxP replacing the deleted gene.

A reference should always be considered for everything it would have fairly taught a person having ordinary skill in the art, whether it teaches way from a claimed invention or supports the patentability thereof.

Luby *et al* fail to either disclose or suggest producing a human Ig of the desired isotype in Sμ deleted transgenic mouse or using the loxP site in the Sμ-deleted (ΔSμ) mouse to insert a transgene in the endogenous mouse IgH locus.

In fact, Luby *et al* confirm the well-established scientific principle in the art of immunology that IgM production is essential for the development of functional B cells which undergo isotype class switching from IgM to the IgG, IgA or IgE isotypes (figures 2 and 3).

However, Luby *et al* disclose that the efficiency of class switching is clearly reduced in the Sμ-deleted mouse (Line 7 of the abstract page 159 and lines 7-8 of the first paragraph page 161; page 162, 1st column, end of 2nd paragraph). More importantly, the switch recombination at Sγ1 and Sγ2 which is used to control switching from IgM to the downstream human IgH of the desired isotype in the Xenomouse of Green is drastically reduced in the in ΔSμ mouse of Luby *et al* as shown by the reduced expression of IgG2b and IgG1 (figure 2B and Table 1). The Figure 2 from Luby *et al* shows also that the serum level of IgM which are not the desired isotype, was increased (figure 2C), while that of the desired isotype was either reduced by two to five folds (IgG) or unchanged (IgA; figure 2A).

It is well-known in the art that the production of transgenic mice is laborious and time consuming as described by Green *et al* (see all the examples of Green *et al* and in particular examples 8, 22, and 29 which relates to the introduction of additional mutations in the transgenic mouse).

Therefore, the ordinary skilled artisan with the aim of producing a pre-selected human antibody isotype (IgA) from a transgenic mouse would only introduce mutations that improve significantly the level of human Ig of the desired isotype that are produced by the transgenic mouse.

The ordinary skilled artisan would not be motivated to introduce mutations that do not change or decrease the level of human Ig of the desired isotype that are produced by the transgenic mouse.

Therefore, the skilled artisan would have been dissuaded to delete Sμ from the IgH locus to produce Ig antibodies of the desired isotype in a transgenic mouse.

Therefore, Luby *et al* teach away from the claimed invention.

However, even assuming, *arguendo*, that the ordinary skilled artisan would have been motivated to combine the teaching of Green *et al* with the teaching of Luby *et al*, the ordinary artisan would have modified the transgenic mouse of Green *et al* by deleting the switch sequence Sμ in the human IgH transgene as taught by Luby et al to arrive at a transgenic mouse containing a human IgH transgene containing: human VH genes, all the human D elements, all human J elements, human Cμ and human Cδ from human chromosome 14, and a human constant region gene encoding the desired IgH isotype operably linked to an heterologous switch region, *i.e.* a transgenic mouse which is as different from the claimed transgenic mouse as the transgenic mouse from Green.

Further assuming, *arguendo*, that the ordinary skilled artisan would have used the ΔSμ mouse of Luby *et al* for expressing human IgA, he would insert the human Cα transgene in place of the mouse Cα gene because, as mentioned by the Examiner on page 5 of the Office Action, switching to IgA is unchanged in the ΔSμ while switching to IgG isotypes is reduced.

Importantly, the skilled artisan would have arrived at a transgenic mouse which is still very different from the claimed transgenic mouse in that the human Cα transgene would replace the mouse Cα and not Sμ as in the claimed transgenic mouse. The transgenic mouse of Luby et al is expected to produce high levels of mouse IgMs, low levels of mouse IgGs (IgG1, IgG2a, IgG2b, IgG3) and low levels of chimeric IgAs which is different from the claimed transgenic mouse which produces high levels of chimeric IgAs, no mouse IgMs and negligible levels of mouse IgGs.

Therefore, by combining the teaching of Green *et al* and Luby *et al*, the skilled artisan would not arrive at the claimed transgenic mouse because none of the prior art documents teaches

replacing Sμ by a human Cα transgene in the mouse endogenous IgH locus.

Even though, the Examiner mentions that the ΔSμ mouse contains a LoxP site downstream of Eμ and upstream of Cμ, providing a universal insertion for any transgene of interest (page 5 of the Office Action), the skilled artisan aiming at producing human IgAs in a transgenic mouse, would have neither inserted a human Cα transgene using this loxP site because he would have recognized immediately that the generated mouse produces no IgM, the expression of the Cμ gene being abolished by the transgene (as shown in figure 1 and on page 7, lines 11-15 of the present application).

As explained above, Green *et al*, Luby *et al* and the established principles in the art of immunology teach away from producing a transgenic mouse which produces no IgM because IgM production in mice is recognized to be essential for the development of functional B cells able to produce antibodies of the desired isotype in response to immunisation with an antigen.

For these reasons, it is considered that the cited prior art and the established scientific principles in the art of immunology clearly teach away from the claimed invention. Moreover, there is nothing of record to rebut the weight of this evidence.

Contrary to the above-mentioned established conventional wisdom in the art of immunology, the present inventors have demonstrated in the present invention that, in the absence of IgM expression, mice can unexpectedly develop functional B cells able to produce chimeric IgA antibodies in response to immunisation with an antigen (Examples 1, page 27, lines 12-23; Example 3, page 37, lines 10-33, figures 1 and 9). None of the cited references would have given one skilled in the art any reason to expect such a result.

Therefore, since even the cited references in combination would have failed to have disclosed or suggested all of the elements of the claimed invention, or have provided a reasonable expectation of success for the present invention, and because these documents teach away from the claimed invention, this rejection is unsustainable and should be withdrawn.

Further to the above, the examiner's attention is directed to *Crocs, Inc. v. US. International Trade Commission, 598 F.3d 1294 (Fed. Cir.2010)*, in which a claimed invention was held by the Federal Circuit to be non-obvious over a combination of prior art references because the prior art was found to teach away from the claimed combination and moreover, the claimed invention was found to yield more than predictable results. These principles are particularly important in the post-*KSR* era in recognizing patentable inventions. Applicants wish to make the following additional remarks in respectful reply to various assertions made by the examiner.

Firts, the above analysis of Green *et al* clearly demonstrates that contrary to the examiner's assertion (page 3 of the Office Action), Green *et al* do not disclose a transgenic mouse for producing specific isotypes of human antibodies whose endogenous mouse IgH locus comprises the replacement of its switch sequence Sμ (mouse endogenous Sμ) by a human Cα gene.

The deletion of mouse endogenous Sμ in the endogenous mouse IgH locus is not supported by the text cited by the examiner (abstract and column 12; page 3 of the Office Action). Furthermore, Sμ is neither deleted in the Xenomouse for the reasons already discussed above.

The human CH gene in Green *et al* includes human Cα for the reasons already discussed above. The cluster of enhancer 3' to the Cα gene in column 13, which is cited by the Examiner (page 4 of the Office Action) is not relevant because it relates to a sequence which is different from the human Cα gene In addition, it is difficult to conceive how the human Cα gene could be necessarily present in the mouse cluster of enhancer 3' to the human Cα gene, which is clearly not the case as shown in figures 1 to 6.

Contrary to the examiner's assertion (page 4 of the Office Action), figure 1 of Green *et al* does not disclose a gene encoding human Ig kappa light chain in a transgenic mouse but the Cγ region structure in the YAC IgH transgene y2Bm and yH1C.

Second, the examiner mentions that Green *et al* describe using the transgenic mouse for producing any desired specific isotypes of human antibodies, wherein the endogenous IgH loci were inactivated (page 4 of the Office Action). Therefore, the examiner herself acknowledges that in the Xenomouse, the human IgH transgene cannot be inserted at the mouse endogenous locus, otherwise the human IgH transgene would be inactivated and the Xenomouse would not produce human antibodies of the desired isotype.

Contrary to the examiner's assertion (page 4 of the Office Action), the vector which is disclosed in column 10 is a human IgH transgene YAC vector (column 10, lines 31 and 33) which is not a targeting vector and therefore does not contain mouse 5' and 3' homology arm sequences flanking Sμ in the mouse IgH locus as the claimed targeting vector (claim 52) for the reasons already discussed above. Furthermore, in said YAC vector which is different from the claimed targeting vector, the loxP sites (column 15-16) are flanking human Cγ genes (column 16, lines 2-16), whereas in the claimed vector, the loxP sites are flanking an expression cassette for a selection marker (claim 56). The vector which is introduced in the ES cells (example 27) is a YAC vector (column 50, lines 10-11) but not a targeting vector for the reasons already discussed above.

The fact that the human heavy chain transgene YAC yH1C containes the heavy chain promoter, Eμ and the palindrome hs3a/hs1,2/hs3b is not pertinent to claim 52 which relates to the human kappa light chain transgene of the claimed transgenic mouse.

As discussed already, the targeting vector which is disclosed in column 15 and columns 12-13 is for targeted replacement on the YAC, yH1C. Therefore, the targeting vector has 5' homology to the region of the human IgH transgene which is between human Sγ2 and Cγ2 and 3' homology to the YAC arm which contain expression cassettes for yeast and mammalian selectable markers (see figure 2 in which the 5' and 3' homology arms are marked with crosses and column 13, line 1 to 9). Therefore, the targeting vector which is

disclosed in column 15 does not contain mouse 5' and 3' Sμ in the mouse IgH locus as the claimed targeting vector (claim 53).

Third, contrary to the examiner's statement on page 6 of the Office Action, the above discussion of Green *et al* clearly demonstrates that the Xenomouse of Green et al is generated by random insertion of an unrearranged human IgH transgene at a locus which is different from the endogenous mouse IgH locus and further comprises the targeted inactivation (knock-out) of the endogenous mouse IgH locus.

Furthermore, the claimed transgenic mouse not only requires, a modified endogenous IgH locus, deletion of endogenous Sμ and human class A Ig Cα gene. The claimed transgenic mouse requires replacement in the endogenous mouse IgH locus, wherein the endogenous mouse Sμ is replaced with a human class A Ig Cα gene.

Fourth, contrary to the examiner's statement on page 7 of the Office Action, the above analysis of Green *et al* clearly demonstrates that the YAC vector (column 10, lines 24-27) is different from a targeting vector and does not contain mouse 5' and 3' homology arm sequences flanking a targeted mouse locus. In addition the targeting vector disclosed in Green *et al* (figure 5-7; column 13, lines 2-7) which target homologous recombination in the YAC vector contains 5' homology located between human Sγ2 and human Cγ2 and 3' targeting homology in the YAC arm as clearly shown in figure 2 (the 5' and 3' homology arms are represented by crosses). As explained in the above analysis the YAC arms carry expression cassettes for yeast and mammalian selectable markers (column 10, lines 31-35). Therefore, the targeting vector of Green *et al* does not contain mouse 5' and 3' homology arm sequences flanking a targeted mouse locus.

Therefore, Green *et al* neither disclose or suggest a targeting vector for targeting homologous recombination in the mouse endogenous IgH locus. Furthermore, Green *et al* neither disclose or suggest a targeting vector for targeting homologous recombination in the regions flanking the endogenous mouse Sμ in the endogenous mouse IgH locus.

As noted above, a reference must always be considered for everything it would have fairly taught a person having ordinary skill in the art. Therefore, the passage on column 2, lines 55-58 which is cited by the examiner should be interpreted in the context of the complete paragraph from lines 55 to 67. This paragraph clearly refers to the combination of random insertion of large human IgH transgenes using YAC vectors with the targeted inactivation of the endogenous mouse IgH locus since Green et al recite "*Another advantage of this approach is that the large number of V genes has been shown to restore full B development* ***in mice deficient in murine immunoglobulin production***", *i.e.*, a mouse which is transgenic for large human IgH fragments and comprises the targeted inactivation of the endogenous mouse IgH locus (see column 6, lines 12-17; column 9, line 58 to column 10, line 20). Attention is directed to the following additional remarks made in reply to the examiner's assertions at pages 6-10 of the Official Action.

1. As explained above, Green *et al* disclose the targeted inactivation of the endogenous IgH locus (mice knock-out at the IgH locus) which is different from the claimed mouse which has a functional IgH locus comprising a targeted gene replacement (mice knock-in at the IgH locus).

2. As acknowledged by the examiner on page 7 of the Office Action, the claimed transgenic mouse requires that the endogenous mouse Sμ in the mouse endogenous mouse IgH locus is replaced by a human class A Ig Cα gene. As explained above, Green *et al* do not disclose or suggest replacement in the endogenous mouse IgH locus, wherein the endogenous mouse Sμ is replaced with a human class A Ig Cα gene. Therefore, the fact that the claims are inclusive that a non-cognate switch region may be present is not relevant because Green *et al* do not teach the claimed targeted gene replacement in the endogenous mouse IgH locus.

   As explained above, the fact that Luby *et al* disclose that Sμ can be deleted is not pertinent for the claimed invention because Luby confirms that antibody class switch is essential for the production of Ig of the desired isotype and also because the prior art teaches away from replacing Sμ by a human CH transgene because the insertion abolishes the expression of Cμ which is essential for the development of functional B cells in mice.

3. The argument has been addressed *supra*.

4. As mentioned above, the prior art documents and the application do need to disclose what is already known in the art and should be read giving the words the meaning and scope which they normally have in the relevant art.

   In the wild-type mouse IgH locus, Sμ is downstream of Eμ and upstream of Cμ (see figure 1 of the present application: "*Endogenous IgH locus in mice*"). Therefore, replacing mouse Sμ by a human Cα transgene results necessarily in the human Cα transgene being inserted between Eμ Cμ in the mouse IgH locus as clearly shown on figure 1 of the present Application ("*murine locus after homologous recombination*").

   Claim 43 and 52 relate to human Ig light transgene comprising Eμ and the mouse 3' enhancer of Green *et al*, which is different from the recombined mouse IgH locus of claim 36.

   The fact that the figures in Green *et al* do not include the position of Cμ is not pertinent because this position is known in the art. As explained above, the unrearranged human IgH transgene disclosed in Green comprises 66 human VH, all the human D elements, all human J elements, human Eμ, **human Sμ, human Cμ,** human Cδ and a chimeric human CH gene in which class switch recombination between Sμ and the human Sγ2 or the mouse Sγ1 controls isotype-class switching from human IgM to the downstream

human CH gene for the desired IgH isotype (Cγ1 or Cγ4 in the exemplified transgenic mouse strains; column 6, lines 26-33; column 11, lines 55, 61; column 12, lines 53-55 and 59-60).

As explained above, Luby *et al* disclose only a Sμ deleted transgenic mouse for studying the role of Sμ in antibody class switching Sμ, wherein a loxP site replaces Sμ.
Luby does not disclose or suggest producing a human Ig of the desired isotype in Sμ deleted transgenic mouse or using the loxP site in the Sμ-deleted (ΔSμ) mouse to insert a transgene in the endogenous mouse IgH locus.
In addition, the prior art teaches away from inserting a human CH gene at the loxP site in the Sμ-deleted (ΔSμ) mouse of Luby for the reasons explained above already.

5. The argument is addressed *infra.*

6. Claim 36 has been modified to specify that the claimed transgenic mouse produces chimeric IgAs but no IgMs.

These limitations are not obvious over Green *et al* in view of Luby *et al* for the reasons explained above.

Example 10 clearly shows that the Xenomouse produces significant baseline levels **of both human IgM and human IgG** in the absence of immunization (page 39, lines 45-47 and Table 6).

Therefore, the Xenomouse produces both IgM and IgG. For expressing human IgG, the Xenomouse requires expression of both human Cμ and Cγ genes from the human IgH transgene.

As explained already, example 10 confirms the well-established scientific principle that **B cell maturation, *in vivo*, requires the expression of membrane IgM on B cells surface and that the production of a selected antibody isotype, *in vivo*, requires the development of IgM producing B cells which subsequently undergo isotype class switching from IgM to the IgG or IgA, or IgE isoptypes. The frequency of class switching increases during an immune response** (see in particular the paragraphs entitled "*XenoMouse Development*", bridging columns 9 and 10; "*B cell Development*, column 10; "*Class Switching*", bridging columns 11 and 12 of Green).

Therefore, contrary to the Examiner's assertion on page 10 of the office Action, expression of IgG, IgA or IgE from the endogenous wild-type IgH locus (Luby) or an unrearranged IgH transgene (Xenomouse of Green) requires isotype switching from IgM to the downstream IgG, IgA or IgE and isotype switching occurs without immunization.

For producing a desired type of antibodies, the prior art teaches to insert the desired human IgH gene operably linked to a switch sequence (Sα, Sγ) downstream of a fragment of the IgH locus comprising V genes, D genes, Eμ, Sμ and Cμ (see Green, in

particular column 6, lines 36). The IgH of the desired isotype are produced upon switching from IgM to the downstream IgH of the desired isotype (Green; column 5, lines 63-64; column 10, lines 16-20 and 61-62; column 22; lines 30-50; Examples 9, 16 (Tables 5 and 10 showing IgM+ B cells); Examples 10, 17 (Tables 6 and 11 showing human IgM and IgG antibodies production).

Therefore, the prior art does not teach expression of antibodies of the desired isotype (IgG, IgA, IgE) without class-switch.

Contrary to the examiner's assertion, one cannot just insert the desired human Ig gene while inactivate endogenous one because IgM are essential for B cell development in mice for the reasons explained before.

Therefore, the prior art teaches away from generating a transgenic mouse which produces no IgMs like the claimed transgenic mouse.

Hence, this ground of rejection is unsustainable and should be withdrawn.

Applicants gratefully acknowledge the withdrawal of the previous ground of rejection against claim 58.

Claims 36-50 and 52 stand rejected under 35 USC 112, first paragraph as ostensibly failing to comply with the written description requirement.

However, in view of the amendment of claim 36, this ground of rejection is deemed moot.

Claims 36-50 and 52 stand rejected under 35 USC 112, first paragraph, as the present specification ostensibly does not describe the invention now claimed.

However, in view of the amendment of claim 36, this ground of rejection is deemed moot.

Claims 36-50 and 52 stand rejected under 35 USC 112, second paragraph, as being ostensibly vague and indefinite.

However, in view of the amendment of claim 36, this ground of rejection is also deemed moot.

Further, it is respectfully submitted that no new matter has been presented with the pending and active claims under consideration.

Accordingly, in view of all of the above, it is believed that this application is now in condition for allowance. Early notice to this effect is earnestly solicited.

Respectfully submitted,

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